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A Novel Therapeutic Approach Using Extracellular Vesicles in Neuro-Ophthalmic Diseases

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ABSTRACT

Neuro-ophthalmic disorders encompass a diverse group of conditions caused by impaired processing of visual information within the brain. These disorders can lead to significant vision impairment, inflammation, and damage to nerve cells, which can greatly diminish a person's quality of life. Exosomes (Exos) are involved in important processes like neuronal signaling, immune response modulation, and clearance of proteins, making them promising candidates for treating neuro-ophthalmic conditions (glaucoma, optic neuropathies, and retinal degeneration). Extracellular vesicles produced from mesenchymal stem cells and neural progenitor cells have shown potential to protect and possibly regenerate retinal ganglion cells, reduce neuroinflammation, and promote neuronal survival. However, there are still challenges to tackle, particularly in improving methods for isolating Exos. This review discusses the biology and functions of Exos, their protective benefits for eye health, and their capacity to revolutionize the treatment of neuro-ophthalmic diseases, helping to meet the urgent needs in this field. ***DOI: 10.22034/IBJ.30.5.274***

Keywords: Gene expression, Hypoxia, MicroRNAs, Neoplasms

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1. INTRODUCTION

According to the World Health Organization, in 2017, there were globally 253 million people with vision impairment, of whom 35 million were completely blind[1]. Disorders that affect the brain's ability to control vision are termed neuro-ophthalmic disorders. There are many causes of these disorders, including trauma, insufficiency of blood supply, poisoning, inflammation, and tumors[2]. Common symptoms include vision impairment, alterations in pupil response, and ocular movement problems. An example of eye diseases is anterior ischemic optic neuropathy (AION), which arises from reduced perfusion of the optic nerve and is characterized by a gray tube appearance within the damaged optic nerve owing to traumatic optic neuropathy[3-5]. Industrial toxins or drug exposure can

also lead to toxic optic neuropathy, highlighting some of the diverse etiological mechanisms of these disorders. Optic neuritis is another disease of this group, which leads to swelling of the optic nerve and is most often associated with multiple sclerosis (MS)[6]. Patients may complain of sudden loss of vision, pain in the eye, and alteration in color vision. In addition, papilledema—an increased appearance of the optic disc due to increased intracranial pressure—may suggest a more serious condition such as a mass or bleeding in the brain. Moreover, tumors affecting the optic chiasm may result in specific visual field losses such as bitemporal hemianopsia, which is commonly seen in patients with pituitary adenomas[7,8]. Additional cortical infarcts can also involve areas responsible for visual comprehension, disrupting normal visual function and leading to higher-order visual deficits. The effects of neuro-ophthalmic diseases are broader than visual impairment. They can have a large effect on a person's quality of life[9]. Conditions such as AION and optic neuritis can cause unilateral blindness, making it difficult for individuals to navigate their environment, interact socially, or work[5,10]. Although these disorders impose a substantial burden, reliable epidemiological estimates of their prevalence in the general population are still lacking. This disparity makes it difficult for healthcare systems to efficiently deploy resources for diagnosis and treatment. To address these challenges, additional research is needed to better understand the risk factors and improve early identification, thereby improving the lives of persons suffering from neuro-ophthalmic illnesses[5,6].

According to the MISEV 2023 guidelines, what are commonly referred to as "Exos" are actually a subtype of small extracellular vesicles (sEVs) originating from the endosomal system. They constitute a subtype of small sEVs, as the diameter of intraluminal vesicles within endosomes typically measures less than 200 nm. Nevertheless, in the absence of definitive evidence for subcellular origin, the term "EVs" is favored over "exosomes," as most studies examine a heterogeneous population of EVs rather than exclusively focusing on Exos[11]. Consistent with MISEV 2023 recommendations, we use the terms EVs/sEVs instead of Exos, since endosomal origin could not be definitively established.

When the plasma membrane of a cell includes multivesicular bodies (MVBs), they are secreted after the formation of endosomal compartments in the cell[12]. These small packages contain several important components, such as metabolites, proteins, lipids, and RNA, therefore representing the characteristics and health conditions of a cell[13,14]. These chemicals are transported in Exos, which allow cells to interact with one another, influencing various biological processes and helping to maintain balance in the body[15,16]. Exos are highly significant in cellular biology for several reasons and are involved in many biological functions[17]. For example, in addition to their critical role in transport pathways, they are involved in the immune system by transporting antigens and modulating immune cells. Tumor-derived Exos can promote tumor growth by inducing angiogenesis, metastasizing cancerous cells, and preventing immunological attacks on the tumor[17,18]. Exos are also very important in health and disease since they help neuronal and glial cell communication and assist in the clearance of damaged proteins in the nervous system[19]. Recent research has suggested that Exos may also be used for the treatment and diagnosis of diseases. Their specific characteristics, such as the easy crossing of cell membranes and their biocompatible nature, make them suitable for targeted treatments[20]. As research into Exos progresses, they have the potential to revolutionize regenerative medicine, cancer treatments, and the field of central nervous system (CNS) problems[15,16,21]. To sum up, Exos play a vital role in cellular biology by acting as messengers between cells and influencing a variety of biological processes[22]. This review aims to increase the understanding of Exo functions to improve diagnostic and therapeutic strategies in neuro-ophthalmic diseases.

2. EXOs: BIOLOGY AND FUNCTION

The endosomal system in cells is responsible for the biogenesis of Exos, a process that is very complex and well-regulated[23]. The process commences with the invasion of the plasma membrane, leading to the formation of early endosomes. These early endosomes advance into late endosomes or MVBs, which are crucial for Exo growth[24]. Inside MVBs, intraluminal vesicles are generated when the membrane structures of the endosome, known as buds, invaginate. This process is governed by endosomal sorting complexes required for transport, which largely enables the encapsulation of certain proteins, lipids, and nucleic acids, such as microRNAs (miRNAs) and messenger RNAs (mRNAs), into these vesicles[25,26]. After their production, MVBs may either fuse with lysosomes for degradation or with the plasma membrane to facilitate the release of sEVs into the extracellular space[16]. Various biological signals determine these choices. The coordination of Exo release through MVB fusion with the plasma membrane allows Exos to be released from the cells and potentially target adjacent cells or even enter the bloodstream[27]. Several factors control the release of Exos; for example, cellular insults such as hypoxia, inflammation, environmental changes, and various signaling pathways, including growth factors and cytokines, ritard or accelerate the release of the content of Exos. The accumulation of Exos may be increased or decreased depending on the activated signaling pathway[23,28,29]. Due to the ever-changing contents of the Exos, which correlate with the physiological conditions of the primary cell, they present a great opportunity to analyze the communication and

functions of cells[29]. The intricate interactions between Exos biogenesis, cellular signaling, and environmental cues are highlighted by the fact that controlling Exo production and secretion is essential for preserving cellular homeostasis and adapting to environmental changes[30]. This connection underscores the importance of Exos in various physiological and pathological circumstances and elucidates their possible functions in both health and disease[22,31]. Exos are fascinating membranous structures that enable intercellular communication, carrying the features of the original cells[32]. These vesicle-like structures, encased in a lipid membrane, contain diverse bioactive components, including proteins, lipids, and nucleic acids[33].

Exos comprise many proteins, including stress-inducible heat shock proteins that facilitate protein folding and confer protection against environmental stress, as well as tetraspanins like CD63 and CD81 that enable intercellular communication. Exos are abundant in phospholipids, cholesterol, and sphingolipids, which contribute to their stability, morphology, and size[32-34]. They also contain genetic materials (such as mRNAs and miRNAs) that can change the gene expression of the target cells[35]. For this reason, they can mediate important biological activities, including immune responses and cellular differentiation[34]. In simpler terms, Exos are effective carriers of information, explaining the great deal of physiological activity in cells[34,35]. Exo roles in transporting vital components are significant for normal cell function, as well as for diagnostics and treatment during pathological processes. Research on Exos provides new insights into understanding cell communication and in developing therapies for several diseases[30,36]. This advancement could increase the scope of Exo therapy in the future. These and other examples demonstrate how nature places cells in contact with each other[33] (Fig. 1).

Exos serve as crucial intermediaries for communication between neurons and glial cells in the CNS, as well as in various other physiological processes[37]. In neuroscience, Exos act as a medium for the translocation of important bioactive compounds that influence the behavior of surrounding cells. For example, neurotrophic factors (NTFs), which support the growth and maintenance of neurons, can be carried in Exos released from neurons[38]. Exos also contain miRNAs involved in several processes, including memory and learning, and can alter certain target genes in recipient cells[37,39-41]. Furthermore, Exos play a vital role in preserving the homeostasis of the nervous system by removing debris and misfolded proteins from cells[42]. This cleanup process is essential because, in neurodegenerative conditions, toxic proteins can build up and disrupt normal functions, such as organelle trafficking and cellular cleanup[40]. Through various mechanisms, Exos contribute to limiting inflammation and protecting neurons by communicating

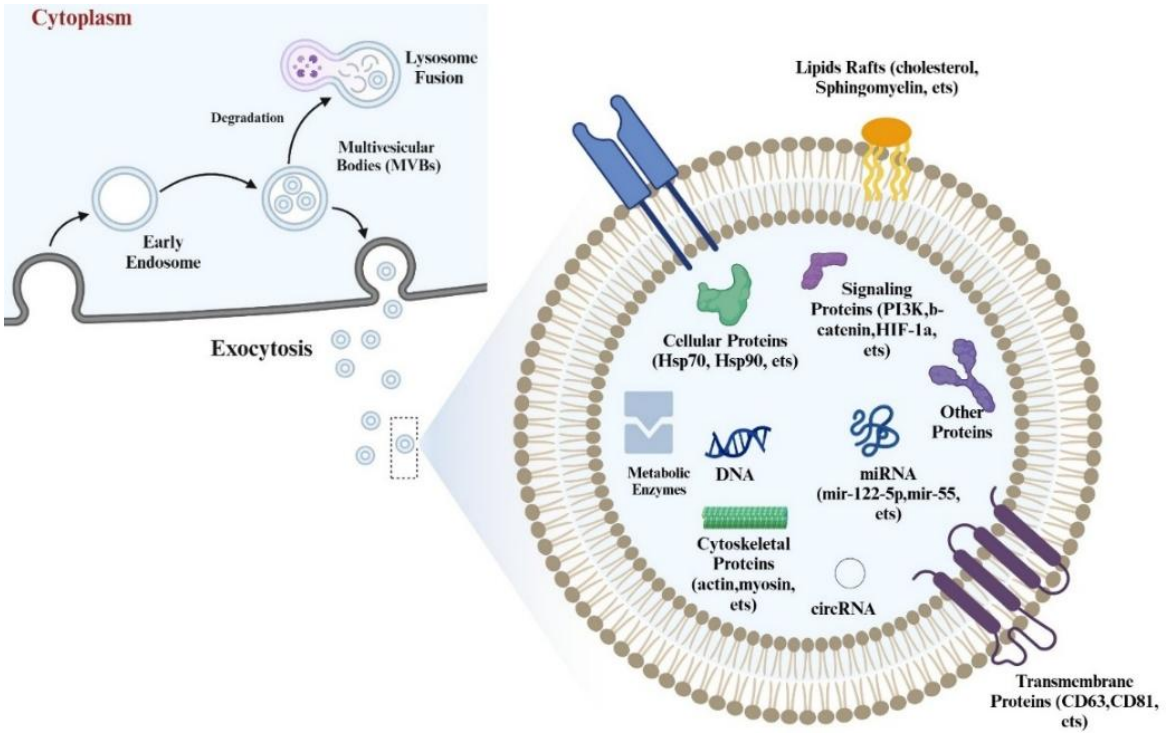

Fig.1. Exos biogenesis, showing the formation of Exos within MVBs and their release via exocytosis, along with a detailed view of their diverse molecular cargo (created in BioRender.com).

with other immune mediators. They are implicated in several disorders affecting the nervous system and its overall health[43]. Imagining the structures and functions of these nano-sized vesicles could provide novel therapeutic approaches for disorders like MS, Parkinson's, or Alzheimer's diseases. They probably will enhance our understanding of the operation of the nervous system and its plasticity[39].

3. EXOs AND NEUROPROTECTION IN GLAUCOMA

Glaucoma is defined by the gradual degeneration of retinal ganglion cells (RGC) due to a multifaceted interplay of vascular, genetic, structural, and immunological factors affecting the optic nerve. This disease is a leading worldwide cause of visual impairment, with diagnosis frequently delayed owing to its silent progression until advanced stages. In 2020, it was reported that 76 million individuals globally would be afflicted with glaucoma, an increase from 57.5 million affected by primary open-angle glaucoma (POAG), with forecasts indicating a further rise to 111.8 million by 2040[44,45]. Glaucoma is classified into various varieties, including primary and secondary forms, which are further divided into open-angle and angle-closure categories. Secondary glaucoma arises from many ocular or systemic conditions[46]. The predominant form of glaucoma is POAG, a condition that advances gradually, leading to diminished outflow of aqueous humor and ultimately resulting in optic nerve injury without an identifiable cause[47]. Recent genetic and genomic studies have provided compelling data suggesting that heredity may play a role in the onset of glaucoma. Genes linked to heightened intraocular pressure (IOP) or an augmented risk of POAG include *ABCA1*, *AFAP1*, *ARHGEF12*, *ATXN2*, *CAV1*, *CDKN2B-AS1*, *FOXC1*, *GAS7*, *GMDS*, *SIX1/SIX6*, *TMCO1*, and *TXNRD2*. Nonetheless, the impact of genetic variables may fluctuate according to environmental conditions. The exact molecular mechanisms of POAG are still unidentified, yet inflammation and aging are probable key factors. Genetic associations have been reported between primary angle-closure glaucoma and variants in *MMP9*, *HGF*, *HSP70*, *MFRP*, and *eNOS*[48]. Normal-tension glaucoma (NTG), characterized by IOP within the normative range of 10-21 mmHg, accounts for approximately 50% of undetected glaucoma cases[49]. Patients with NTG are more prone to have undergone significant shock or prolonged hypotension, indicating a possible involvement of optic nerve ischemia in the pathogenesis of NTG[50]. Research has demonstrated that NTG patients with silent brain infarcts have an increased risk of visual field deterioration. The pathophysiology of NTG remains incompletely elucidated[51]and lowering IOP remains the primary treatment and offers advantageous results for these individuals[52]. Neurodegenerative pathways in glaucoma encompass oxidative stress, axonal transport dysfunction, neuroinflammation, excitotoxicity, and autophagy[53]. Elevated IOP in glaucoma injures the optic nerve by compressing its arterioles, resulting in hypoxia-induced mitochondrial impairment, diminished neurotrophic support, and microglial activation, which triggers inflammation and activates the complement cascade[54]. Mutations in the *OPTN* gene result in excessive glutamate and overstimulation of NMDA receptors, leading to excitotoxicity due to abnormalities in glutamate transport. The role of autophagy as either a protective or detrimental mechanism is under examination. Glaucoma exhibits similarities with other neurodegenerative disorders like Alzheimer's and Parkinson's diseases, suggesting the possibility of comparable therapeutic approaches[47,55,56].

3.1. Role of EXOs in protecting RGCs

Mesenchymal stem cells (MSCs) are multipotent stromal cells capable of self-renewal and differentiation. These cells can be extracted from various mesenchymal tissues, such as bone marrow stem cells (BMSCs)[57], adipose tissue[58], dental pulp[59]and umbilical cord blood[60], in addition to other sources. Research on MSCs has demonstrated encouraging outcomes in facilitating the protection and regeneration of CNS neurons. The retina, an extension of the brain and a component of the CNS, has analogous regenerative problems[61]. In a previous study on rat models, researchers proved that BMSC transplantation improved RGC survival[62].

3.2. MSC-derived EVs (MSC-EVs) in optic nerve crush (ONC) and RGC survival

The small size of EVs may be beneficial for the protection and regeneration of RGCs. Studies have demonstrated that only particles measuring between 50 and 200 nm can access the retina after an intravitreal injection. Larger particles, by contrast, generally remain within the trabecular meshwork and vitreous cavity[63-65]. A recent study has demonstrated that intravitreal infusion of MSC-EVs enhanced the survival of RGCs in rats subjected to ONC. This intervention diminished the concentrations of pro-inflammatory cytokines (tumor necrosis factor-alpha, IL-1β, IL-6, IL-8, monocyte chemotactic protein-1) and increased the levels of the anti-inflammatory cytokine IL-10. MSC-EVs also decreased apoptosis induced by ONC by augmenting the Bcl-2/Bax ratio and decreasing caspase-3 activity[66]. The observed effects indicate that MSC-EVs mitigate RGC apoptosis and inflammation, potentially through the activation of the PI3K/AKT

pathway in this experimental ONC model[66,67]. In another rat ONC model, treatment with umbilical MSC-derived EVs (UMSC-EVs) significantly enhanced the survival of Brn3a-immunopositive RGCs and activated GFAP+ glial cells in both the retina and optic nerve. However, UMSC-EVs did not increase GAP43+ axon counts in the optic nerve. This observation suggests that while UMSC-EVs provide neuroprotection by supporting RGC survival and glial cell activation, they do not promote axon regeneration[68]. Conversely, BMSC-EVs significantly promoted both RGC survival and axon regeneration, while also partially preventing axonal loss and RGC dysfunction. These EVs effectively delivered their cargo to the inner layers of the retina. The therapeutic effects of these EVs are dependent on miRNA activity. Argonaute-2, a crucial miRNA effector, showed reduced efficacy following its knockdown. Moreover, inhibiting specific NTF receptors led to reduced neuroprotective and neurogenic effects, which emphasizes the significance of NTFs as demonstrated by the NTF-enriched EVs from MSCs[69].

3.3. Therapeutic effects of MSC-EVs in retinal degeneration (rd10 models)

The protective effects of MSC-EVs on the retinas of rd10 mice have been investigated in Zhang et al.'s study. Human umbilical cord MSCs were extracted from umbilical cord tissue, and MSC-EVs were injected into the vitreous of rd10 animals on postnatal days 14 and 21. The types of retinal cells that absorbed MSC-EVs were subsequently examined. At 24 hours following the injection, MSC-EVs diffused into all retinal layers, including the outer nuclear layer (ONL), inner nuclear layer, and ganglion cell layer, showing that practically all retinal cells could endocytose these vesicles. Immunofluorescence studies on retinal whole-mounts revealed that astrocytes endocytosed essentially no MSC-EVs, although retinal microglia/macrophages and *Müller* glia did[70]. The normal saline-treated rd10 retina significantly reduced its ONL thickness compared to the wild-type retina, and treatment with MSC-EVs significantly improved the thickness of the ONL. For example, at 600 μm distant from the center of the optic disc, the ONL thickness of the normal saline-treated group was 6.5 ± 0.3 μm, while MSC-EVs treatment increased it to 12.0 ± 0.8 μm. Thus, MSC-EVs therapy reduced photoreceptor loss in rd10 animals. Reactive gliosis in the retina is a sign of inflammation, evidenced by increased GFAP levels in Müller glial cells and the activation of microglia/macrophages. Because reactive gliosis appears in rd10 mice as early as postnatal day 10, they investigated whether MSC-EVs suppress the activation of microglia/macrophage and Müller glial cells in the rd10 retina by immunostaining for Iba1 (microglia/macrophage), F4/80 (M0 macrophage), CD63 (M1 macrophage), CD206 (M2 macrophage), and GFAP (Müller glial). Furthermore, MSC-EVs significantly boosted the mRNA expression of the anti-inflammatory cytokine arginase 1, while the pro-inflammatory cytokines Areg and Nr4a3 were downregulated[70-72]. MSC-EVs decreased inflammation in the rd10 retina; hence, using RNA sequencing, they discovered that MSC-EVs changed the transcriptome of the genes linked to immunity and inflammation. This sequencing technique also screened 13 genes linked to immunity and inflammation among the 40 differentially expressed genes identified between the NS-treated and MSC-EV-treated rd10 retinas. Additionally, MSC-EVs were shown to block the NF-κB signaling cascade in rd10 retina, reducing apoptosis and inflammation in vitro. The treated animals also exhibited a thicker ONL, where photoreceptors reside. However, in the MSC-EV-treated animals, improved photoreceptor survival was indicated[70].

3.4. MSC-derived vesicles in diabetic retinopathy (DR)

A study revealed that BMSC-EVs upregulated miR-486-3p, which provides protective effects in DR mice by inhibiting the TLR4/NF-Kb signaling pathway. While TLR4 and NF-κB were highly expressed in high-glucose-treated Müller cells, miR-486-3p was poorly expressed[73]. A separate study demonstrated that MSC-sEVs were administered intravitreally to diabetic rats to evaluate their therapeutic efficacy. The findings indicated that MSC-sEVs decreased DR by transmitting miR-22-3p, which suppresses the activation of the NLRP3 inflammasome[74].

3.5. MSC-EVs in ocular hypertension and hypoxic preconditioning

In a recent study, Evangelho et al. demonstrated that intravitreal transplantation of human Wharton's jelly-MSCs in rabbit models enabled the early detection of changes in the optic nerve head using optical coherence tomography in an experimental model of ocular hypertension. Structural improvements, such as an increase in optic cup volume, were observed in this model[75]. It is notable that hypoxia-preconditioned (Hyp)-sEVs had greater therapeutic potential for improving retinal structure and function and reducing photoreceptor apoptosis, compared to normoxic sEVs. This enhancement is due to the delivery of higher levels of GAP43 in Hyp-sEVs. The activation of hypoxia-inducible factor-1α by hypoxic preconditioning inhibits TRIM25-mediated ubiquitination and degradation of GAP43, leading to its increased presence in Hyp-sEVs[76] (Fig. 2 and Table1).

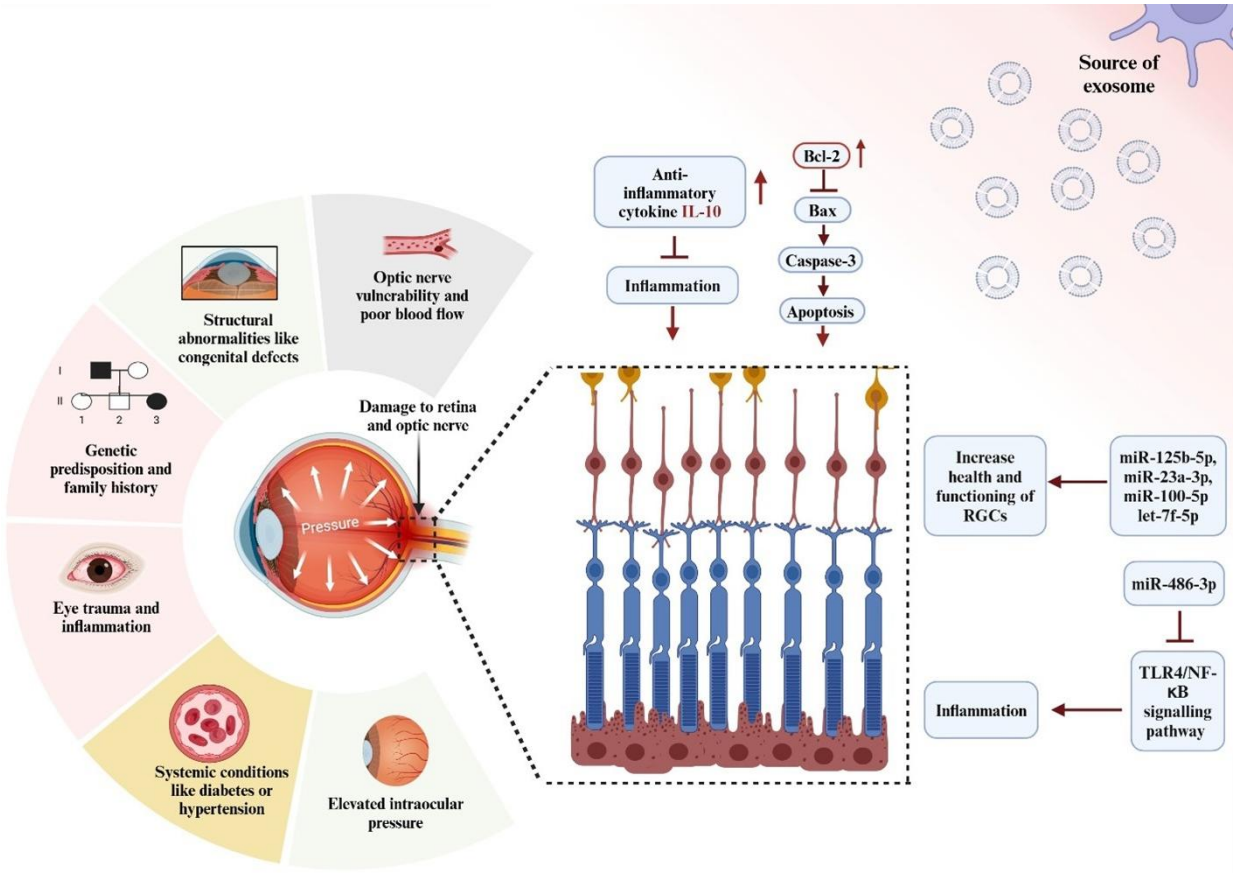

Fig. 2. Role of EVs in retinal health and disease, highlighting various factors contributing to retinal damage and potential EV-mediated therapeutic interventions (created in BioRender.com).

4. EVs IN THE TREATMENT OF OPTIC NEUROPATHY

Optic neuropathy, commonly observed in ophthalmology, manifests with multiple etiological causes. A fast emergence of symptoms typically suggests demyelinating, inflammatory, ischemic, or traumatic causes[77]. In contrast, a gradual decline in visual acuity is typically linked to compressive lesions, toxic or nutritional deficits, and genetic disorders[78,79]. Optic neuritis occurs more commonly in females, with incidence increasing between the ages of 30 and 40 years[80]. This condition can be the initial symptom in approximately 25% of MS cases and occurs during the disease progression in around 70% of patients, primarily during the relapsing-remitting phase. Advancements in magnetic resonance imaging (MRI) have enhanced diagnostic capabilities, facilitating the identification of dissemination in both spatial and temporal contexts. This advancement enables the diagnosis of MS at the onset of acute optic neuritis in specific patients[81]. Leber hereditary optic neuropathy is a maternally inherited mitochondrial disorder marked by significant and progressive bilateral vision impairment. This condition arises from the selective degeneration of RGCs[82]. Dysfunction of the optic nerve may also result from exposure to many pharmaceuticals, poisons, and nutritional inadequacies[83]. The primary contributors to this condition are ethambutol, amiodarone, methanol, ethanol, and tobacco[83,84]. Paraneoplastic syndromes are a collection of uncommon immune-mediated illnesses linked to cancer[85]. Paraneoplastic optic neuropathy (PON) may initially manifest as isolated unilateral or bilateral optic neuropathy, frequently accompanied by other neurological problems[86]. PON is predominantly associated with small-cell lung carcinoma, but it has also been correlated with other neoplasms, including B-cell lymphoma, cutaneous melanoma, pancreatic glucagonoma, neuroblastoma, uterine sarcoma, and various carcinomas (such as those of the breast, prostate, nasopharynx, papillary thyroid, non-small cell lung, and renal cell)[87]. In systemic malignancies such as lymphoma, leukemia, multiple myeloma, and carcinoma, infiltration of the optic nerve may occur[88]. The optic disc may present as either enlarged or normal. MRI scans of the brain and orbit may demonstrate enhancement of the meninges and optic nerve[89,90].

Table 1. Summary of MSC-EV cargo, their cellular targets, and the related signaling pathways in retinal protection

Source of EVs	Key cargo	Target cell	Signaling pathway	Main therapeutic effect	Reference
BMSC	NTFs (e.g., brain-derived NTF)	RGCs	Not Specified	Neuroprotection and neurogenesis	[62,69]
MSC-EVs	Bcl-2/Bax ratio	RGCs	PI3K/AKT	Decreased apoptosis and inflammation	[66,67]
UMSC-EVs	Brn3a markers	RGCs	Not Specified	Enhanced RGC survival	[68]
MSC-EVs	Arginase 1	Microglia	M1/M2 polarization	Reduced reactive gliosis	[70-72]
MSC-EVs	Transcriptome genes	Retinal cells	NF-κB signaling	Blocked apoptosis and inflammation	[70]
BMSC-EVs	miR-486-3p	Müller cells	TLR4/NF-κB	Protection in diabetic retinopathy	[73]
MSC-sEVs	miR-22-3p	Retinal cells	NLRP3 inflammasome	Suppression of inflammation in DR	[74]
Human Wharton's jelly-MSCs	Unspecified (total EVs cargo)	RGC axons	Not specified	Structural improvements in optic nerve head	[75]
Hyp-sEVs	GAP43	Photoreceptors	Hypoxia-inducible factor-α/TRIM25	Reduced apoptosis and improved function	[76]

One more category of optic neuropathy is traumatic optic neuropathy, which occurs when the optic nerves experience direct or indirect trauma. This type of injury can result in partial or even permanent vision loss, primarily because it causes significant harm to the RGCs and their connecting fibers[91]. A distinct form of optic neuropathy is inflammatory (non-demyelinating) optic neuropathy. This category includes many disorders in which the optic nerve is affected by ocular or systemic inflammation[92]. Optic disc edema frequently accompanies posterior uveitis and retinitis. Therefore, while assessing optic disc edema, it is advantageous to examine for indications of inflammation in both the anterior and posterior segments of the eye. Additionally, optic neuropathy may manifest as a component of orbital inflammatory disorders, including orbital pseudotumor[93,94]. Neuromyelitis optica spectrum disorder is an uncommon, antibody-mediated condition of the CNS characterized by intense inflammation of the spinal cord, optic neuritis, and, in some cases, persistent vomiting and hiccups[95]. Visual loss in NMOSD is frequently severe and bilateral, and it may occur either before or after the onset of myelopathy[96]. Non-arteritic AION is a significant cause of visual impairment in middle-aged and elderly patients, characterized by abrupt, painless vision loss and enlargement of the optic disc[97]. It is believed that it arises from ischemia at the optic nerve head; however, its precise etiology remains ambiguous. Non-arteritic AION generally impacts those over the age of 50 who possess tiny optic discs and exhibit vascular risk factors[97,98]. AION is a significant visual impairment that necessitates differentiation between arteritic AION, induced by giant cell arteritis, and non-arteritic AION[99]. Giant cell arteritis constitutes a medical emergency owing to the imminent risk of swift, bilateral blindness, which can frequently be averted via fast and vigorous intervention[100]. Accurate differentiation between arteritic and non-arteritic AION necessitates the assessment of systemic and visual manifestations of giant cell arteritis, increased erythrocyte sedimentation rate and C-reactive protein, substantial visual impairment, optic disc edema, cilio-retinal artery occlusion, choroidal non-filling on fluorescein angiography, and temporal artery biopsy[101,102].

A further example of optic neuropathy is compressive optic neuropathy. It is a condition in which mechanical pressure damages the RGC axons of the optic nerve, leading to a gradual and painless deterioration of optic nerve function and structure. The compressive masses causing this condition can vary widely in type, size, growth rate, and systemic impacts[103]. BMSCs and UMSC-EVs synthesize and release miRNAs required for the growth and survival of RGCs[104]. The important miRNAs consist of miR-143-3p, miR-10b-5p, miR-486-

5p, miR-22-3p, and miR-21-5p, which are released by the BMSCs through EVs. Interestingly, UMSC-derived EVs contain miR-21-5p as well as other important miRNAs, including miR-125b-5p, miR-23a-3p, miR-100-5p, and let-7f-5p. Collectively, these miRNAs help maintain the health and function of RGCs. Collectively, these miRNAs help maintain the health and functionality of RGCs[105,106]. miR-17-92, an exosomal miRNA derived from BMSCs, suppresses the expression of phosphatase and tensin homolog, which is crucial in limiting the expansion and survival of RGC axons. This approach highlights the regulatory function of exosomal miRNAs in target cells and illustrates the potential application of EVs in neuroprotection and regenerative medicine[107]. In an experiment, researchers induced retinal damage in animals using lasers and subsequently injected MSC-EVs into the vitreous cavity. Their findings indicated that these EVs effectively reduced immune cell infiltration, specifically CD68-positive cells, inhibited RGC apoptosis, and alleviated retinal damage by decreasing the expression of monocyte chemotactic protein-1[108]. Bian et al. discovered that EVs derived from neural progenitor cells (NPC-EVs) could diminish the activation of retinal microglia, thereby safeguarding photoreceptors against apoptosis in a model of retinal degeneration. Both mouse-derived NPC-EVs and human-derived NPC-EVs encompassed 17 distinct miRNAs that predominantly target inflammatory pathways associated with tumor necrosis factor-alpha, IL-1β, and COX-2, leading to the deactivation of microglia. These data indicate that NPC-EVs may contribute to the therapeutic advantages of NPC transplantation and could represent a viable treatment alternative for retinal degeneration[109]. Now, we would like to present more examples of the therapeutic applications of EVs in neuro-ophthalmic diseases, though these are based on non-human studies. Administering mouse MSC-EVs intravitreally in a mouse model of retinal ischemia-reperfusion injury led to the microcapsules accumulating in the inferior vitreous cavity. The microcapsules released EVs for more than a month during their degradation, resulting in the retinal thickness nearly reverting to a healthy condition[110]. By intravitreally injecting hypoxia-cultured EVs containing angiogenically active components from human MSCs, with saline as a control, the impact of EVs on retinal ischemia was demonstrated in mouse models of oxygen-induced retinopathy. EV therapy reduced retinal ischemia and prevented retinal thinning compared to the control group[111]. Also, regularly administering BMSC-EVs produced positive neuroprotective effects. However, additional dose-response research will be necessary to ascertain the ideal amount and frequency of treatment. In addition to the therapeutic properties of EVs, their uptake efficiency by ocular cells is also important. In a 2021 in vivo study by Mathew et al., they investigated the uptake and distribution of BMSC-EVs in the retina. They found that EVs injected into the vitreous or applied as ex vivo retinal explants were absorbed by astrocytes, microglia, Müller cells, and retinal neurons. It must be noted that the maintenance of the EVs varied among different retinal cells, with the longest duration observed in RGCs, where they remained for up to 14 days in vivo. Importantly, no toxicity was detected in the retina following EV administration[112]. All these data underscore the therapeutic potential of EVs in RGCs, which is summarized in Table 2.

5. EVs AS THERAPEUTIC CARRIERS

The conventional approach to treating eye diseases, especially in the anterior region, involves the topical administration of eye drops, which has disadvantages such as the necessity for frequent dosing and limited bioavailability. In recent years, many synthetic drug carriers have been developed to encapsulate existing medications to enhance their therapeutic efficacy[113]. However, concerns regarding their immunotoxicity and rapid clearance by the mononuclear phagocyte system remain[114,115]. EVs have some similarities with other drug delivery systems, but they also have some capabilities that distinguish them from other drug delivery systems and make them unique. For example, EVs have a bilayer lipid membrane that surrounds an aqueous core[116]. This structure allows them to be loaded with both water-soluble and fat-soluble substances for delivery to specific target locations[117]. Also, EVs can easily spread in biological fluids, persist in the bloodstream for extended periods, and be absorbed by recipient cells through natural physiological barriers[118]. Although EVs tend to accumulate in organs such as the liver, spleen, and lungs following systemic administration, they still exhibit inherently low immunogenicity and generally do not trigger significant immune responses[118,119]. EVs can be delivered using various methods depending on the specific disorder, such as intravenous injection[120], oral administration[121], intravitreal injection[111], direct injection to the tumors[122], and intraperitoneal injection[123]. Regardless of their intended application, EVs must be extracted from diverse and complex biological samples[124]. EVs derived from 293 T cells producing adeno-associated virus type 2 were considered reliable tools for intravitreal gene transfer into the retina. They have exhibited greater efficiency in retinal transduction compared to conventional adeno-associated virus type 2 after intravitreal injection[125]. Pituitary adenylate cyclase-activating polypeptide

Table 2. Therapeutic effects of stem cell-derived EVs in protecting and repairing retinal neurons in nerve injury models

Model study	EVs source	Findings	Reference
Optic nerve injury (rat)	MSC	Intravitreal injection of MSC-EVs could reduce RGC apoptosis and inflammation in part through the PI3K/AKT pathway.	[66]
ONC (rat)	UMSC	Intravitreal injection of UMSC-EVs increased RGCs' survival but did not improve axon regeneration at 21 days post-treatment.	[68]
ONC (rat)	BMSC	BMSC-derived EVs protected RGCs through miRNA rather than protein content, providing considerable therapeutic benefits.	[69]
Retinitis pigmentosa (mouse)	MSC	MSC-EVs primarily exert their effects by modulating inflammation mediated through the miR-146a-5p–*Nr4a3* axis, thereby maintaining retinal structure and function in rd10 animals.	[70]
DR (mouse)	BMSC	The upregulation of miR-486-3p, produced by EVs originating from BMSCs, exerted a protective effect in DR mice through the suppression of the TLR4/NF-κB axis.	[126]
DR (in vitro/in vivo [rat])	MSC	MSC-sEVs mitigated DR via transmitting miR-22-3p to suppress NLRP3 inflammasome activation.	[74]
Retinal degeneration (mouse)	MSC	Hyp-sEVs showed improved therapeutic potential to prevent photoreceptor apoptosis and enhance structural and functional degeneration of the retina.	[76]
Retinal degeneration (RD) (mouse and rat)	NPC	In an RD model, grafted NPC-EVs effectively inhibited retinal microglia activity to provide protection against NPC-induced photoreceptor death.	[109]
Retinal ischemia (mouse)	MSC	Intravitreal delivery of EVs made from human MSCs reduced the degree of retinal ischemia and was well tolerated without immunosuppression.	[111]
Uptake and distribution of administered BMSC-EVs (rat)	BMSC	EVs introduced into the vitreous or applied as an ex vivo retinal explant were detected in astrocytes, microglia, Müller cells, and retinal neurons.	[112]
Age-related macular degeneration ([in vitro/in vivo (rat)])	Adipose tissue MSC	The protective effects of adipose tissue MSC-EVs against Aβ42 retinotoxicity were investigated.	[127]
retinal ischaemia-reperfusion injury (mouse)	MSC	EVs localized in the inferior vitreous cavity generated EVs for about one month during their degradation, subsequently restoring retinal thickness to nearly normal levels.	[110]

(PACAP) is a multifunctional peptide initially identified in the hypothalamus of sheep[128]. It belongs to the glucagon/secretin superfamily, which also includes vasoactive intestinal peptide, secretin, peptide histidine isoleucine, and growth hormone-releasing hormone. PACAP exists in two forms: PACAP-38, with 38 amino acids, and PACAP-27, with 27 amino acids. PACAP-38 is the predominant form, accounting for about 90% of total PACAP in the body[129]. Research has indicated that EVs can transport PACAP-38 via CP05 (EVPACAP38) and effectively deliver this neuropeptide to the retina in a rat model of traumatic optic neuropathy. Treatment with EVPACAP38 enhanced the survival of RGCs and promoted axon regeneration following damage[63].

6. FUTURE DIRECTIONS AND RESEARCH PERSPECTIVES

EV-based drug delivery has some benefits over alternative drug delivery methods, including less immunogenicity and improved bloodstream stability. Furthermore, the membranes of EVs can be modified to exhibit epitopes that attach to ligands on particular cell types, increasing the effectiveness of drug delivery. Based on these unique features, EVs are effective vector systems for precise drug delivery[130,131]. EVs also participate in regulating the morpho-functional integrity of the retina at various levels. The secretome of retinal cell types, particularly retinal pigment epithelium and Müller glial cells, is essential in this regulatory process. Researchers have suggested that changes in the secretory functions of these cells may influence the development and progression of retinal diseases[132]. Notwithstanding its numerous advantages, obstacles persist. One major issue is the isolation of EVs; while there are multiple approaches, a consistent strategy for procuring clinical-grade EVs has yet to be established. Moreover, directing EVs to particular cells poses an additional challenge. The mechanisms that control this targeting process remain incompletely elucidated, although factors such as surface chemicals, the physiological state of target cells, and the method of administration are crucial determinants[133]. Technologies for the delivery of nucleic acids utilizing EV mimics have been developed. One method entails producing size-controllable EV mimics by progressively extruding non-tumorigenic MCF10A cells through filters with varying pore sizes, thereafter encapsulating siRNA using electroporation[134]. Several companies are in the clinical stages of developing EV-based therapeutics. Codiak Biosciences is a biotech startup focused on creating EV therapies, including therapeutic EVs designed to deliver siRNA targeting the KRAS (G12D) mutation in pancreatic cancer[135]. The company has recently obtained FDA approval for an investigational new drug application to initiate a phase Ia/b trial for patients with pancreatic cancer (NCT03608631)[136] (Fig. 3).

7. CHALLENGES OF USING EXOs IN NEUROTHERAPY

The lack of industrial standards is a major obstacle to the commercialization of EVs. They point out that EVs from various sources have distinct characteristics, necessitating different manufacturing protocols and quality control measures[137]. Furthermore, the stability, safety, potency, and overall quality of EVs must be carefully monitored during both production and shipping. Therefore, they recommend a set of standards to address all these aspects, which will need advancements in technology and coordination between government and industry regulations[137]. A group of

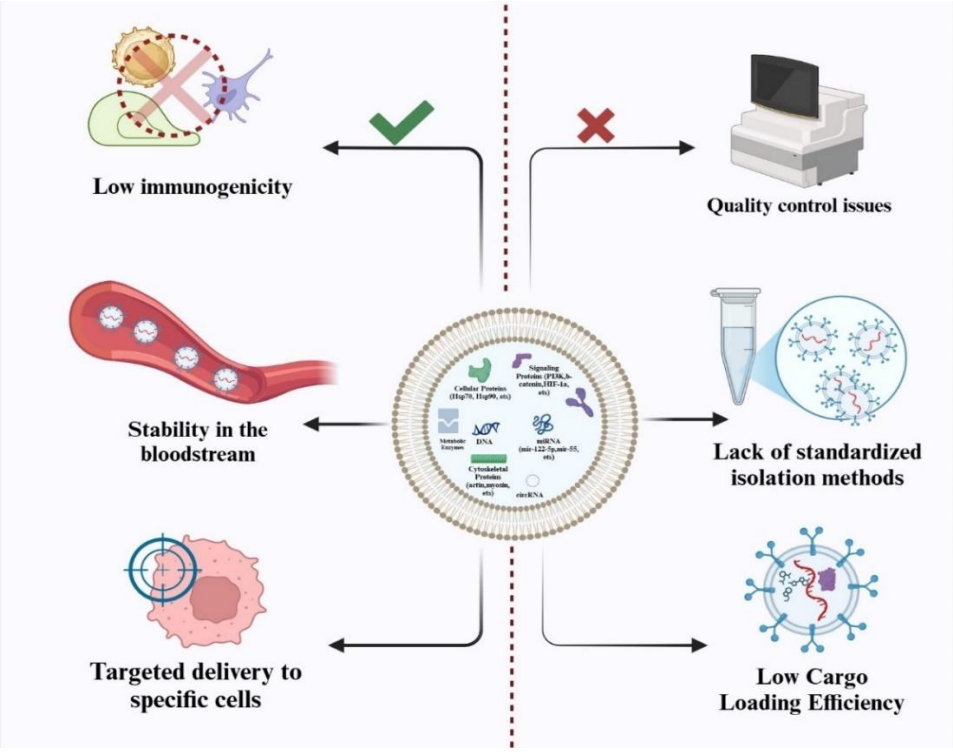

Fig. 3. Challenges and benefits of using EVs (created in BioRender.com).

researchers suggested that standardizing EV dosage and potency across studies can improve data reliability, which can help the government set the rules for standardization[138]. Despite efforts to optimize production, evolving federal guidelines remain a challenge for clinical translation. However, as the heterogeneity of EVs becomes better understood, researchers believe that EVs will become more reproducible and easier to apply in biological therapies[138]. In agreement with MISEV2023 recommendations, we highlight the major challenges limiting the clinical translation of EVs-based therapeutics, including heterogeneity, scalability of production, storage instability, dosing standardization, and regulatory considerations[139]. In spite of advancements in laboratory research on EVs, their clinical application is still in early stages. A limited number of clinical trials are examining the efficacy and safety of EV-based therapies. The lack of extensive randomized controlled trials significantly hinders the wider implementation of EV-therapies in clinical settings. Clinical trials for prostate and lung cancer remain in early stages, necessitating further validation of the efficacy, safety, and overall applicability of these therapies. Challenges encompass identifying optimal dosage, determining the administration route, and establishing biomarkers for predicting responses to EV therapy. Moreover, the long-term efficacy and potential side effects of these treatments remain inadequately understood, which is essential for developing standardized treatment protocols. Addressing these challenges necessitates thorough clinical studies that assess both immediate therapeutic benefits and potential long-term risks. Systematic clinical research is crucial for establishing a robust basis for the incorporation of EV-based therapies into standard cancer treatment protocols[140]. From our perspective, the transition of EV therapy from preclinical models to ophthalmic clinical practice faces a “valley of death” that requires resolution through three strategic pillars. MISEV 2023 stresses that standardizing isolation methods is not only a technological necessity but also a requirement for regulatory approval. Secondly, we believe that the future lies in specialized bioengineering. Instead of using "natural" EVs, adding ligands unique to the retina onto their surface could greatly lower the dose needed and the negative effects associated with high intraocular pressure. In the end, using artificial intelligence to explain the complex cargo-target interactome will be very important for developing individualized "cell-free" treatments for visual neuropathies.

8. CONCLUSION

EVs, as naturally produced nanosized vesicles, can deliver therapeutic agents to RGCs and the optic nerve with improved bioavailability, and their effects can be monitored and controlled via miRNA-based regulation. Although not yet tested in humans for neuro-ophthalmic diseases, EV-based therapy represents a promising, safe, and efficient targeted approach, pending further research to confirm its safety and cost-benefit before clinical application.

DECLARATION

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Generative AI and AI-assisted technologies

The authors employed Quillbot to improve the English language, grammar, and spelling of the text. This tool was used to enhance the language and make sure the material was clear. The authors are fully responsible for the original ideas and the final content of the published work.

Ethical approval

The procedure used in this study was carried out at Kermanshah University of Medical Sciences, Kermanshah, Iran (ethical code: IR.KUMS.REC.1404.205).

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Authors’ contributions

AY: Writing–review & editing, Writing–original draft, formal analysis, conceptualization; MMFT: writing–original draft, formal analysis, data curation, conceptualization; SP, ZM, and ZRM: writing–original draft, conceptualization; GR and LR: project design and management, writing–review & editing, writing–original draft, conceptualization.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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